RESEARCH ARTICLE

EVALUATION OF ANALGESIC EFFECT OF XYLAZINE, TRAMADOL AND LIGNOCAINE ON PROPOFOL ANAESTHESIA IN WEST AFRICAN DWARF (WAD) GOAT

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ABSTRACT

Twenty clinically healthy matured male West African Dwarf (WAD) goats aged 10 to 12 months with a mean weight (±SEM) of 17.5 kg were randomly assigned to four groups A, B, C, and D of five goats per group. The groups A, B, C and D received normal saline (2 ml IV), xylazine (0.05 mg/kg body weight [b/w] intravenously [IV]), tramadol (2 mg/kg b/w IV) and lignocaine (2.5 mg/kg b/w, subcutaneous infiltration at surgical area [SC]), respectively. Each goat in all the groups was anaesthetized with propofol at 9 mg/kg body weight (b/w) and maintained at 6 mg/kg b/w bolus administration. Laparotomy was performed on each goat in each group. Anesthetic indices and vital parameters were measured. Propofol alone (group A), and propofol/tramadol combination (group C) provided a short duration of analgesia despite high maintenance doses and quantity of propofol used in the groups. However, propofol/ xylazine combination (group B) provided analgesic duration enough to perform laparotomy, while propofol/ lignocaine combination (group C) provided the longest duration of action. Both lignocaine and xylazine combinations provided enough analgesia for the surgical procedure in this study. However, xylazine combination was associated more with prolonged sleeping, recumbent and recovery time, cardiac and respiratory depression, which are undesirable in ruminants due to the resultant cardiopulmonary and gastrointestinal complications. Lignocaine has more stabilizing effect on cardiac functions in addition to moderate sleeping, recumbent and recovery time. Hence, lignocaine with the long duration of analgesia, hemodynamic effects, and moderate anesthetic indices may be preferred among other selected drugs as a better combination agent with propofol for induction of anesthesia prior to apainful surgical procedure in West African dwarf (WAD) goat.

Keywords: Analgesia, lignocain, propofol, tramadol, WAD goat, xylazine

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INTRODUCTION

General anesthesia in ruminants, especially in sheep and goats, using propofol anesthesia has been advocated (Dzikitas et al., 2013; Ukwueze et al 2014). Propofol-induced anesthesia has desirable qualities, including fast recovery and non-cumulative effects upon repeated administration (Hall, et al., 2001; Dzikitas, 2013). However, the use of propofol as a sole drug to induce anesthesia is not sufficient, especially for noxious surgical procedure, due to its poor analgesic property (Ospina et al., 2024). This deficiency can be supplemented through drug combinations to produce balanced anesthesia. Balanced anesthesia can be achieved with the use of more than one anesthetic drug or with premedication (Hall, et al., 2001).

Premedication is a practice of administration of some drugs prior to induction of anesthesia with the aim of reducing the dose, complementing the effects and counteracting the side effects of the induction agents (Geel, 1991, Sheen et al., 2014). This improves the quality of anesthesia and facilitates the achievement of balanced anesthesia (Marviya et al., 2020; Moore et al., 2024). The use of different class of drugs such as opioids, alpha-2-adenoreceptor agonists, local anesthetics in premedication, especially during propofol induced anesthesia, has been documented (Abrahamsen, 2008; Sheen et al., 2014). Opioids such as Pentazocine and Tramadol provide analgesia for moderate and severe pain by actions in the central nervous system (Sameer and Neeran, 2011). Xylazine, an alpha-2-adenoreceptor agonist produces analgesic, sedative and muscle relaxant effects (Fereidoon et al., 2005; Ukwueze et al., 2014), while lignocaine provide regional or local analgesia and has antiarrhythmic effects (Yalamuru et al., 2022; Silva et al., 2023).

Propofol is known to combine well with different drugs. The combination of propofol with xylazine, tramadol, ketamine and lignocaine has been reported in dogs, cats, and goats (Geel, 1991; Ajadi et al., 2012; Tanaka et al., 2015; Weinberg et al., 2015; Gupta and Bhalotra, 2019; Hammadet al., 2020). However, determination of the most effective drug combination is imperative to ensure potent analgesia and fewer side effects.

The main objective of this study was to evaluate the efficacy of xylazine, tramadol, and lignocaine as premedicants during propofol anesthesia in West African Dwarf goats (WAD).

MATERIALS AND METHODS

Animals used

Twenty (n = 20) healthy male WAD goats with average age (±SEM) 12 months, and average weight (±SEM) 17.5 kilograms were used for this study. The animals were acclimatized for three weeks during which they were evaluated and stabilized for surgery prior to the beginning of the study. When the animals arrived to the college facilities, they were thoroughly examined for apparent signs and symptoms of illness. Blood samples were collected and examined for the presence of blood parasites. Feacal samples were collected from each animal and examined for helminth ova. The animals were dewormed with levamisol injection (Hebei Huarun Pharmacy ltd China) and also treated with antibiotic, oxytetracycline (Chongqing Bull Animal Pharmaceutical Co., Ltd) 10% short acting for 3 consecutive days at 1 ml per 10kg intramuscularly to safeguard against bacterial infections. They were also vaccinated against Peste des Petits ruminatum (PPR) virus using PPR vaccine from National Veterinary Research Institute, Vom. Jos, Plateau State, Nigeria. The animals were kept in well-ventilated, concrete floor and aluminum-roofed animal house at the college facilities. The wall of the house was constructed with blocks up to one quarter, and the remaining height with wire gauze allowing the light period of 12 hours. The goats were kept in clean pens with bedding. They were fed with grasses and feed concentrates, and water was provided *ad libitum*.

Ethical approval

Ethical approval was granted by the College of Veterinary Medicine Research Ethics Committee, Michael Okpara University of Agriculture, Umudike, Abia State, Nigeria (MOUAU/CVM/REC/202410). Animal welfare was ensured in accordance with the Helsinki Declaration of 1975 and its revised edition from 1983, while also respecting the International Statute on Experiments Conducted on Humans and Animals.

Drugs used

Drugs used in the study were propofol (Pofol, 1% Dongkook Pharmaceuticals, Korea), xylazine (Kepro Ltd., Holland), tramadol (Makcur Laboratory Ltd. Gajarat, India) and lignocaine (Nama Pharmaceutical drug, Mumbai).

Criteria for premedicant drug selection

The drugs were selected based on the properties of the individual drugs as follows:

1. Xylazine (sedative): analgesic, muscle relaxant and CNS depressant.
2. Tramadol (opioid): analgesic, CNS depressant.
3. Lignocaine: (local anesthetic): analgesic, antiarrhythmic

Experimental design

The healthy male goats were randomly assigned into four groups A, B, C, and D of five goats each. Group A served as control in all the experiments.

The groups A, B, C and D received normal saline (2 ml, IV), xylazine (0.05 mg/kg body weight IV), tramadol (2 mg / kg IV), lignocaine (2.5 mg / kg SC), respectively, as premedicants. Each goat in all the groups was anaesthetized with propofol at 9 mg/kg body weight (b/w), and anesthesia was maintained at 6 mg / kg b/w bolus administration. Laparotomy was performed on each goat.

Surgical procedure (Laparotomy)

The animal were fasted prior to surgery. Food was withheld for 18 hours and water for 12hours. The goat in each group were prepared for normal aseptic surgery. The hairs around left flank region of the goats were thoroughly clipped. The proposed surgical site was scrubbed with chlorhexidine gluconate B. P. 0.3% W/V (Purit®, Saro Lifecare Limited, Lagos, Nigeria).

Each goat was placed on right lateral recumbency to expose the left flank. Laparotomy was done according to a standard procedure described by (Ames, 2007; Hendrickson, 2007).

The surgical incision was closed routinely from inside out; peritoneum and muscle layers were closed with atraumatic needle and chromic catgut, size 1 (Agary Pharmaceuticals Ltd, Xinghuai, China) using simple continuous suture pattern. The subcutaneous layer was closed with chromic catgut, size 2 and atraumatic 1/2 circle taper point needle (Agary Pharmaceuticals Ltd, Xinghuai, China) using simple continuous suture pattern. The skin was closed using interrupted horizontal mattress suture pattern with nylon (Agary Pharmaceuticals Ltd, Xinghuai, China).

Post-operative analgesic was given to all the animals used in the study irrespective of the group it belonged. Diclofenac sodium 2.5 mg/kg, body weight was administered intramuscularly.

Anesthetic indices

Modified method of determination of anesthetic indices (Adetunji et al., 2002) was used. The onset of anesthesia, analgesic duration, sleeping time, recumbent time and standing time were recorded following administration of the anesthetics using a modified method of determination of anesthetic indices (Adetunji et al., 2002).

Analgesic duration:

This was determined by recording the time of disappearance of flank twitch as sign of loss of pain using a needle prick before the beginning of the surgery and also recording the time of appearance of pain using pain responses: muscle twitch, body movement and vocalization during the surgery.

The difference between the time of disappearance (TD) and the time of reappearance (TA) of flank twitch reflex gives the analgesic duration. TA – TD = AD

Physiologic parameters

The following physiological parameters were monitored: heart rate, respiratory rate and rectal temperature.The parameters were recorded before the induction of anesthesia at time zero (0 min) and, subsequently, at every ten minutes (10 min) interval post induction throughout the period of anesthesia. The parameters were observed and recorded manually as well as electronically using Veterinary multi-parameter patient monitor, ARI-800C (ARI medical equipment Co, Ltd, Zing, Hong Kong)

Data analysis

All the data obtained in these experiments were analyzed using one-way Analysis of Variance and presented as mean ± standard error of the mean. The variant means were separated by the least significant difference of the different groups. Significance was accepted at the level of $P < 0.05$.

RESULTS

Anesthetic indices

The time of onset of propofol was less than 0.60 mins (1 min) in all the groups. It was 0.58 ± 0.01 min (58 seconds) in propofol alone, 0.54 ± 0.02 min (54 seconds) in xylazine/propofol group, 0.59 ± 0.01min (59 seconds) in tramadol/propofol group and 0.59 ± 0.00 min (59 seconds) in lignocaine/propofol group. The onset was significantly ($p < 0.05$) shorter in xylazine/propofol group when compared to the control and other groups (Figure 1). The mean onset of propofol anesthesia was the same in all the groups except in group B, which was significantly shorter when compared to the control group A and other groups.

The mean analgesic period recorded in group D was significantly ($p < 0.05$) longer followed by group B, when compared to the control group A and other groups (Figure 2).

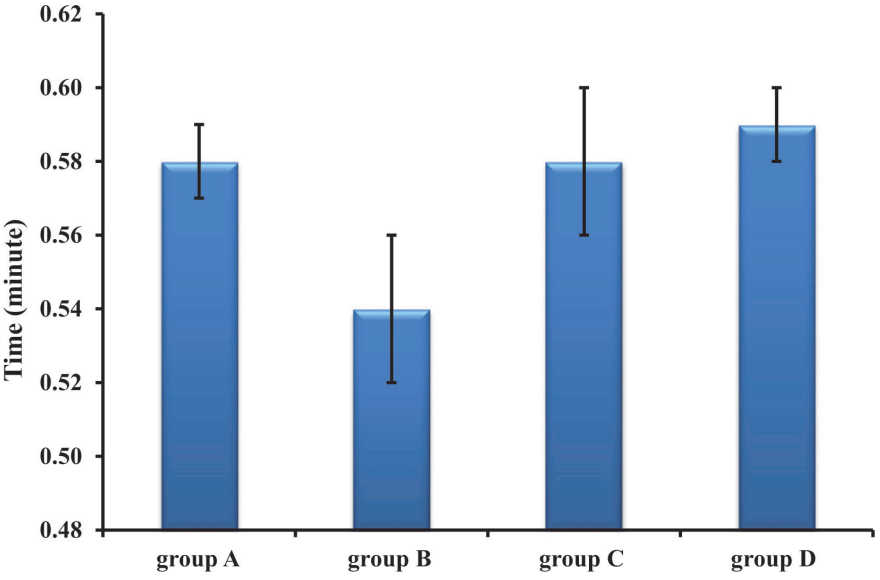
The mean sleeping time was significantly ($p < 0.05$) longer in groups B and D, but shorter in group C when compared to the control and other groups (Figure 3).

The mean recumbent time was significantly ($p < 0.05$) longer in group B, but shorter in group C when compared to the control and other groups (Figure 4).

The mean standing time was significantly ($p < 0.05$) long in group B when compared to the control group A and other groups (Figure 5)

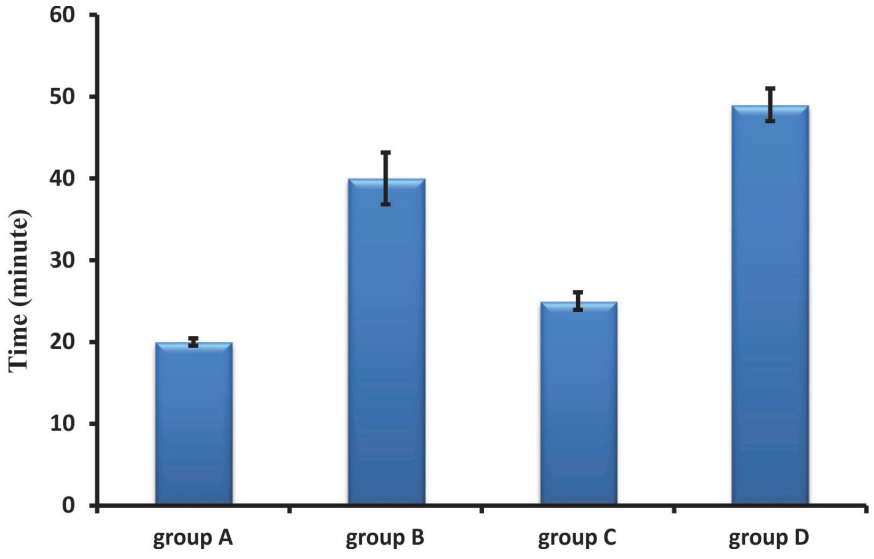
Anesthetic maintenance

The number of times anesthesia was maintained and the quantity of drugs used were significantly higher in the control group A when compared to other groups. However, the number of maintenance and the quantity of drug used were lower in group D followed by group B when compared to the control group A, and the other groups (Table 1).



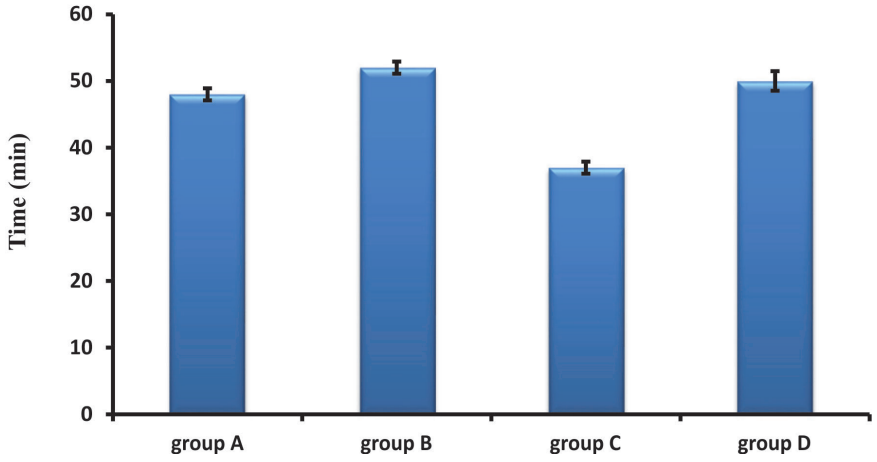
Group A: propofol alone. **Group B: xylazine/propofol.**
Group C: tramadol/ propofol. **Group D: lignocaine/ propofol.**

Figure 1 Mean (±SEM) Onset of anesthesia in goat undergone laparotomy following iIntravenous administration of propofol combinations



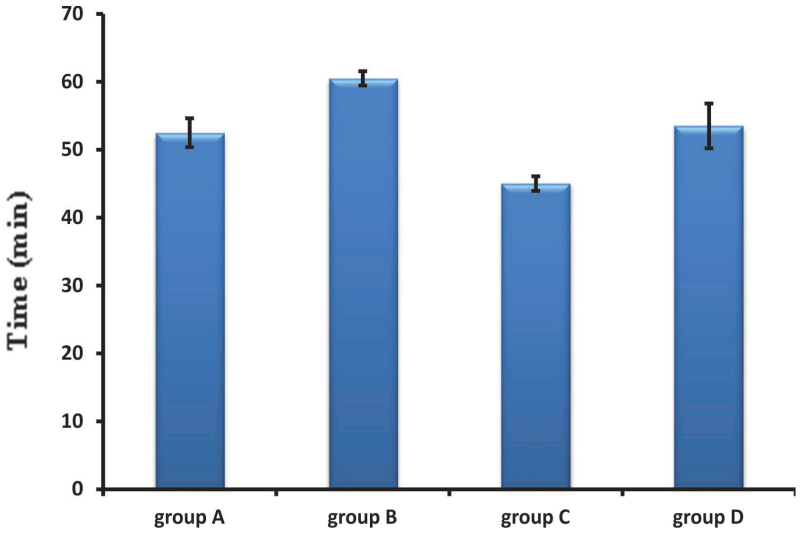
Group A: propofol alone. **Group B: xylazine/propofol.**
Group C: tramadol/ propofol . **Group D: lignocaine/ propofol.**

Figure 2 Mean (±SEM) Analgesic period in goat undergone laporatomy following intravenous administration of propofol combinations



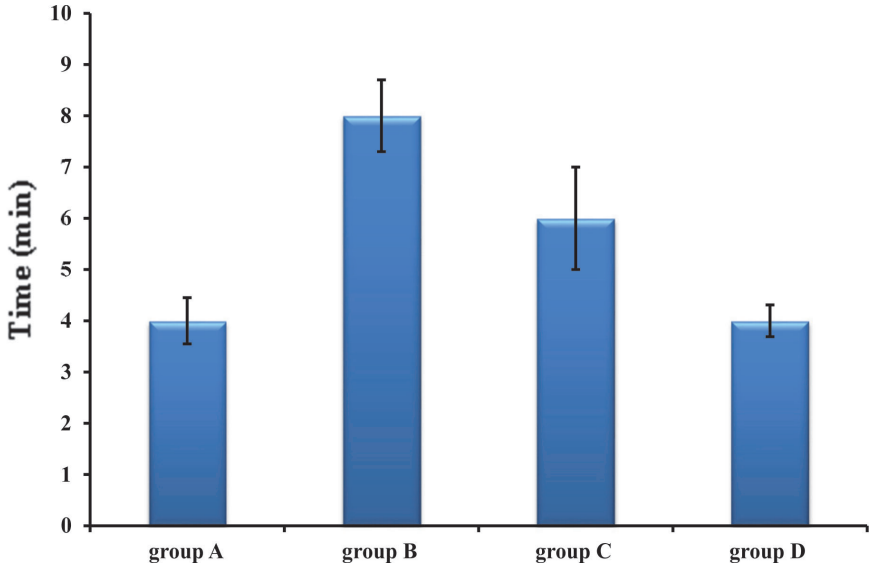
Group A: propofol alone. **Group B: xylazine/propofol.**
Group C: tramadol/ propofol. **Group D: lignocaine/ propofol.**

Figure 3 Mean (±SEM) Sleeping time in goat undergone laporatomy following intravenous administration of propofol combinations



Group A: propofol alone. **Group B: xylazine/propofol.**
Group C: tramadol/ propofol. **Group D: lignocaine/ propofol.**

Figure 4
Mean (±SEM) recumbent time in goat undergone laporatomy following intravenous administration of propofol combinations



Group A: propofol alone. **Group B: xylazine/propofol.**
Group C: tramadol/ propofol. **Group D: lignocaine/ propofol.**

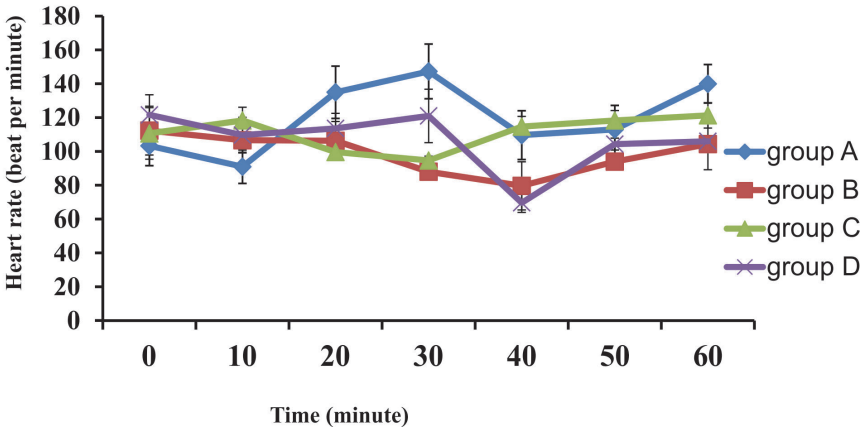
Figure 4 Mean (±SEM) Standing time in goat undergone laporatomy following intravenous administration of propofol combinations

Physiological parameters

The mean heart rate increased significantly ($p < 0.05$) in group C at 40 min post induction when compared to the control and the other groups. However, the mean heart rate was significantly ($p < 0.05$) low in groups B and D at 60 min post induction when compared to the control. Within the groups, the mean heart rate decreases significantly ($p < 0.05$) in groups B and D at 40 min post induction when compared to the baseline value of the groups (Figure 5).

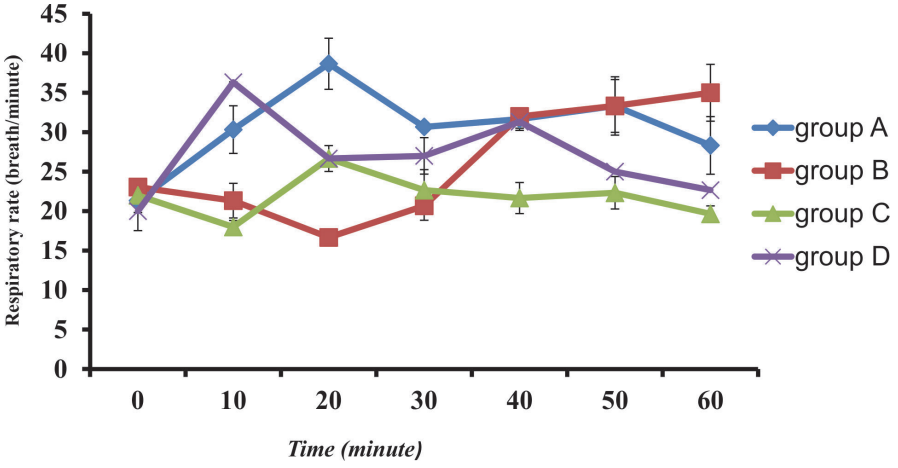
The mean respiratory rate increased significantly ($p < 0.05$) in control groups (propofol alone) at 20 min post induction when compared to other groups. However, the respiratory rate was significantly ($p < 0.05$) low in groups B and C at 30 min post induction and in group C at 40 min post induction when compared to control and other groups. Within the group, the respiratory rate was significantly ($p < 0.05$) high in control group at 20 and 50 min, and in group D from 10 min to 40 min post induction, respectively, when compared to the baseline value of the groups (Figure 6).

The mean rectal temperature of the goats increased significantly ($p < 0.05$) in groups B and D at 20 min, 50 min and 60 min post induction, respectively, when compared to the control group. However, the rectal temperature of goats in group C decreased significantly ($p < 0.05$) at 40 min post induction when compared to the control and other groups. The rectal temperature of goats in group C has no significant ($p > 0.05$) variation except at 40 min post induction when compared to the control group. However, it was significantly low from 10 min to 60 min post induction when compared to groups B and D (Figure 7).



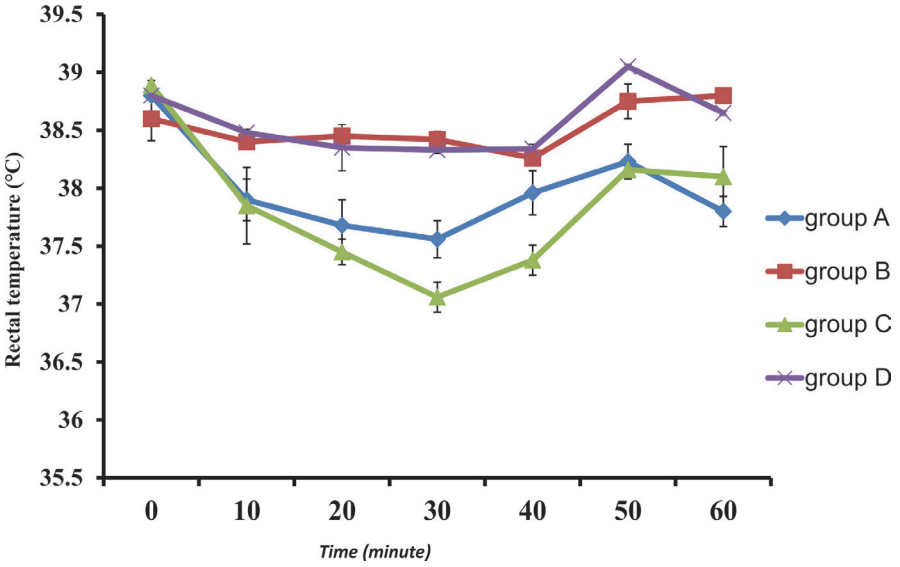
Group A: propofol alone. **Group B: xylazine/propofol.**
Group C: tramadol/ propofol. **Group D: lignocaine/ propofol.**

Figure 5 Mean (±SEM) heart rate of goat undergone laparotomy following intravenous administration of propofol combinations



Group A: propofol alone. **Group B: xylazine/propofol.**
Group C: tramadol/ propofol. **Group D: lignocaine/ propofol.**

Figure 6 Mean (±SEM) respiratory rate of goat undergone laparotomy following intravenous administration of propofol combination



Group A: propofol alone. **Group B: xylazine/propofol.**
Group C: tramadol/ propofol. **Group D: lignocaine/ propofol.**

Figure 7 Mean (±SEM) rectal temperature of goat undergone laparotomy following intravenous administration of propofol combinations

Table 1 Mean (SEM±) anesthetic maintenance following intravenous administration propofol combinations

Group	No. of maintenance	Quantity of drug (mls)
A	4.00 ± 0.12^{d}	17.00 ± 0.85^{d}
B	2.00 ± 0.06^{b}	8.82 ± 0.30^{b}
C	3.00 ± 0.11^{c}	13.42 ± 0.53^{c}
D	1.00 ± 0.08^{a}	4.35 ± 0.10^{a}

^{abc} figures with different superscripts in the same column are significantly different ($p < 0.05$)

DISCUSSION AND CONCLUSION

Propofol administration is known to provide short onset and duration of anesthesia, no analgesia, and a smooth and rapid recovery (Sha et al., 2013; Ukwueze et al., 2014, and Potliya et al., 2015).

The onset of propofol anesthesia in this study was short (> 1 min). Rapid onset of action is caused by rapid uptake of propofol into the central nervous system (CNS) and induction of depression that occur by enhancing the effect of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) and decreasing the brains metabolic activity (Maravi et al., 2018). However, the onset of action was shorter in the group premedicated with xylazine (group B) than in other groups. This may be attributed to sedative and depressive effect of xylazine on CNS (Potliya et al., 2015; Carvalho et al., 2016, and Bayramoglu et al., 2016) before the administration of propofol. In addition, the synergistic and additive interaction between propofol and xylazine at the level of sedation and induction, respectively, may lead to a very short onset of action time observed (Naser and Mohammad, 2014).

Propofol has little or no analgesic properties (Potliya et al., 2015; Desai et al., 2016, and Karacaer et al., 2018). This was confirmed in this study where the use of propofol alone in group A provides short duration of analgesia despite high maintenance doses and quantity of propofol used in the group. However, propofol combination with xylazine and lignocaine provides analgesic duration enough to perform laparotomy. The duration of analgesia was quite longer with xylazine and lignocaine combinations than that of tramadol, while propofol combination with lignocaine provided the longest duration of action. Xylazine provides analgesia through its action on the autonomic and central nervous system (Biobaku et al., 2016). Its inhibition of locus coeruleus neurons in the pons of the lower brain stem, which attenuate the sympathoadrenal responses to noxious stimuli encountered during anesthesia and surgery, and provide hemodynamic, metabolic and hormonal stability (Potliya et al., 2015, and Bayramoglu et al., 2016). Xylazine reduces the release of noradrenalin and dopamine in the central nervous system; thus, it leads to sedation, muscular relaxation and reduction of perception of painful stimuli (Bayramoglu et al., 2016). Longer duration of analgesia, along with prolonged recovery time, was reported in dogs after premedication of propofol with xylazine (Sharma and Bhardwaj, 2010; Potliya et al., 2015). Conversely, lignocaine, amid a group of local anesthetics, provides analgesia by blocking a nerve fiber impulse through binding and inhibition of voltage-gated sodium channels (Raphael et al., 2002) and thereby provides analgesia that lasted up to 54.3 ± 5.2 minutes. Furthermore, there is no receptors competition or interaction between lignocaine and propofol (Tafur-Betancourt, 2017), and the rate of absorption and elimination of lignocaine is slow due to adrenaline incorporation (Weinberg et al., 2015). These factors might be responsible and may explain the findings in this study.

Sleeping and recumbent time were longer in the xylazine group (group B) and shorter in the tramadol group (group C). The longer sleeping and recumbent duration in group B may be a result of sedative and muscle relaxant effect of the xylazine (Shah et al. 2013, and Potliya et al., 2015). Tramadol has been reported to cause central nervous depression in humans, cat, dogs, and horse (Jong-pil Seo et al., 2011). Contrarily, in this study, no obvious sign of CNS depression was observed after administration of tramadol prior to administration of propofol; rather, excitement was observed. Short duration of sleeping and recumbent time was also observed following propofol administration. Though, it is a known fact that opioids decrease sleep time and efficiency (Barber, 2011, and Dimsdale et al., 2007).

Standing time, the period it takes an animal to stand up following anesthesia is an indicator that the animal is approaching almost full recovery stage of anesthesia. The use of propofol alone as in group A was associated with a short period of standing time due to its known fast recovery property (Ukwueze et al., 2014; Potliya et al., 2015), while xylazine combination prolonged the standing time when compared to other combinations used in this study. The prolonged standing time may be attributed to a hypnotic and powerful central muscular relaxant

effect of xylazine, leading to muscle weakness and fatigue (Ahmad et al., 2018). Tramadol also causes sensory and motor nerve conduction blockade, mediated through voltage-gated sodium channels leading to the axonal blockade (Gupta and Bhalotra, 2019). Lignocaine may have more effect on sensory nerve than locomotors nerve hence the short standing time compared to other groups.

The significant increase in the heart rate of groups A (propofol alone) and C (tramadol) during laparotomy procedure may be a result of increased pain stimuli emanating from the laparotomy incision. This showed that propofol alone and in the combination with tramadol did not provide enough analgesia during laparotomy procedure. An increased heart rate is one of the signs of nociception in both human and animal (Sacco et al., 2013), especially when decrease in the heart rate is expected. This also shows that pain response may alter the depressive effect of drugs on cardiac function.

The administration of propofol alone and propofol combinations used in this study depressed respiratory function of the goats leading to apnea. Propofol has a respiratory depressant effect (Ukwueze et al., 2014; Potliya et al., 2015, and Shanovic et al., 2018). However, propofol in combination with xylazine caused more obvious significant respiratory depression due to the combined depressive effect of both drugs on the respiratory center of the brain (Ukwueze et al., 2014). Alpha-2 agonists induce prolonged depression of thermoregulation and depress hypothalamic noradrenergic alpha-2 adrenergic receptors to cause hypothermia (Kumar et al., 2018). It is very important to take note of this serious complication in the use of propofol and xylazine combination. The cause of increase in respiratory rate in the control group (propofol alone) during laparotomy procedure despite the high quantity of anesthetic maintenance used, may also be attributed to pain stimuli because of the laparotomy procedure.

The decrease in the rectal temperature in the xylazine / propofol combination was in accordance with previous findings (Brohi et al., 2019; Ukwueze et al., 2014; Amarpal et al., 2002, and Carroll et al., 1998). The reduction in rectal temperature is considered secondary to CNS depression and reduction in the muscular activity (Kammar et al., 2014). Both drugs may have a depressive effect on the thermoregulatory center of the brain (Maravi et al., 2018). Tramadol and lignocaine have less depressive effect on temperature (Habiban et al., 2011; Ayman et al., 2015, and Ajadi et al., 2017). They seem to have a stabilizing effect on the propofol thermoregulatory depressive effect, as observed in this study. However, the significant drop in temperature at 40 min post induction in tramadol/propofol combination might be a result of the overriding effect of propofol against tramadol probably due to the large volume of the propofol used in anesthetic maintenance in that group.

The duration of analgesia was quite long with xylazine combination and short in tramadol combination, while propofol combination with lignocaine provided the longest duration of action. Sleeping, recumbent and standing time were longest in the xylazine group (group B), followed by lignocaine group and shortest in the tramadol group (group C). Both decrease and increase in physiologic parameters were observed more in xylazine and tramadol combinations than in the lignocaine combination which had more stable hemodynamic effects. Therefore, lignocaine combination significantly ($p < 0.05$) provided better analgesic, anesthetic and hemodynamic effects with moderate sleeping, recumbent and standing time when combined with propofol for induction of anesthesia during laparotomy in West Africa Dwarf goat.

CONFLICT OF INTEREST

The authors declare no competing interests.

CONTRIBUTION

Concept – OCU, CAE, AAO; Design – OCU, CAE, AAO; Supervision - CAE, AAO; Materials – OCU; Data Collection and Processing – OCU; Interpretation – CAE, AAO; Literature Search – OCU; Writing Manuscripts – OCU; Critical Review - CAE, AAO

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EVALUACIJA ANALGEZIČKOG EFEKTA KSILAZINA, TRAMADOLA I LIGNOKAINA NA ANESTETIK PROPOFOL KOD ZAPADNOAFRIČKE PATULJASTE KOZE (WAD)

SAŽETAK

Dvadeset klinički zdravih zrelih mužjaka zapadnoafričke patuljaste koze (WAD) starih između 10 i 12 mjeseci sa srednjom težinom (±SEM) od 17.5 kg je randomizirano u četiri grupe, A, B, C i D sa po pet koza u svakoj. Grupe A, B, C i D su primile fiziološku otopinu (2 ml IV), ksilazin (0.05 mg/kg tjelesne težine (TT) intravenski [IV]), tramadol (2 mg/kg TT IV) i lignokain (2.5 mg/kg TT, subkutana infiltracija u operativnom području [SC]). Sve koze iz svih grupa su anestezirane sa propofolom u dozi od 9 mg/kg TT, dok je doza održavanja iznosila 6 mg/kg TT u bolusu. Na svim kozama iz svih grupa je izvedena laparotomija. Mjereni su anesteziološki indeksi i vitalni parametri. Sam propofol (grupa A) i kombinacija propofol/tramadol (grupa C) su izazvali kratkotrajnu analegeziju uprkos visokim dozama održavanja i količni propofola koja je korištena u grupama. Međutim, kombinacija propofol/ksilazine (grupa B) je izazvala analgeziju koja je trajala dovoljno za laparotomiju, dok je kombinacija propofol/lignokain (grupa C) imala najduže djelovanje. U našem istraživanju, kombinacije i lignokaina i ksilazina su izazvale dostatnu analgeziju za izvođenje operativne procudur. Kombinacija ksilazina je, međutim, povezana sa prolongiranim snom, dužinom ležanja i oporavka, i kardijalnom i respiratornom depresijom koje su kod preživača nepoželjne jer izazivaju kardiopulmonalne i gastrointestinalne komplikacije. Osim što izaziva umjereno spavanje i vrijeme ležanja i oporavka, lignokain ima stabilizirajući efekt na kardijalne funkcije. Stoga se lignokain koji izaziva dugotrajniju analgeziju, hemodinamske efekte i umjerene anesteziološke indekse smatra anestetikom izbora u odnosu na druge lijekove kao kombinirani agens sa propofolom za indukciju anestezije prije izvođenja bolnih operativnih procedura kod zapadnoafričke patuljaste koze (WAD).

Ključne riječi: Analgezija, ksilazin lignokain, propofol, tramadol, WAD koza